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Biomarkers associated with obstructive sleep apnea and morbidities: a scoping review

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Highlights

- The majority of OSA-related biomarkers have relied on blood-based assays.
- Plasma IL-6 and CRP emerge as promising morbidity biomarkers in both adults and children.
- Urinary neurotransmitters identify cognitive morbidity in children with OSA.

Abstract

Objective: To map potential biomarkers of obstructive sleep apnea (OSA)-associated morbidities in both adults and children, to identify gaps in current evidence, and to determine the value of conducting a full systematic review.

Methods: A scoping review was undertaken of studies in patients with OSA that evaluated the potential value of biological markers in identifying OSA-associated morbidities. Retained articles were only those studies whose main objective was to identify morbidity biomarkers in subjects with OSA, the latter being confirmed with a full overnight polysomnography (PSG) in a laboratory or at-home settings. The methodology of the selected studies was classified using an adaptation of the evidence quality criteria recommended by the American Academy of Pediatrics. Additionally the biomarkers were categorized according to their potential clinical applicability.

Results: 572 citations were identified of which 48 met inclusion criteria. Thirty-four studies were conducted in adults and 14 involved children. Most of the studies evaluated blood biomarkers, and presented 31 potential diagnostic biomarkers.

Conclusion: The majority of studies were performed explored blood-based biomarkers, with most not identifying definitive morbidity biomarkers. Of the potentially promising morbidity biomarkers, plasma IL-6 and high sensitivity C-reactive protein appear to exhibit a favorable

profile, and may discriminate OSA patients with and without morbidities in both adults, as well as MRP 8/14 in children. Urinary neurotransmitters may also provide a good tool for screening OSA cognitive morbidity in children.

Keywords: review, sleep apnea, biomarkers, morbidity

Abbreviations

OSA=obstructive sleep apnea

CVD=cardiovascular disease

DTA= diagnostic test accuracy

EDS= excessive daytime sleepiness

PSG= polysomnography

EBC= exhaled breath condensate

RR=risk ratio

OR=odds ratio

AHI=apnea hypopnea index

OAI= obstructive apnea index

RDI= respiratory disturbance index

Hr/TST=hour of total sleep time

ROC= receiver operating characteristic

AASM=American Academy of Sleep Medicine

hsCRP=high-sensitivity C-reactive protein

IGF= Insulin-like growth factor

MRP=myeloid-related protein

IL-6=interleukin-6

1 Introduction

Obstructive sleep apnea (OSA) has now been recognized as a major public health issue with potential society-wide consequences involving car or work-related accidents, cognitive and behavioral deficits impairing work performance, and potentially leading to cardiovascular and metabolic dysfunction. [1] Indeed, OSA has been associated with serious morbidities such as endothelial dysfunction [2,3], hypertension [4], cardiovascular disease (CVD)[5-7], cognitive and behavioral dysfunction[8], metabolic disorders such as insulin resistance [9], diabetes[10], and dyslipidemias[11], erectile dysfunction in men, [12], nocturnal enuresis in children[13], and excessive daytime sleepiness (EDS)[14,15]. Consequently, healthcare costs are substantially increased in patients with OSA, accounting either directly or via its associated morbidities for a substantial proportion of all medical-related costs. [16-18]

In adults, the prevalence of OSA varies widely, from 14.7% to 36.5%, depending on age, gender and ethnicity. [19] It is generally higher in males, [19] and although the prevalence in Hispanics is similar to white Caucasians, it is significantly higher in African American or Asians. [19] In children, the prevalence of OSA is reported as ranging between 1 and 4%.[20,21]

Current diagnostic approaches range from exclusively using clinical presentation and physical

examination to the current 'gold standard', the overnight polysomnography (PSG). However, the measures derived from PSG are poor predictors of OSA-associated morbidities. [22] In other words, two patients with similar OSA severity may present with markedly different clinical phenotypes, whereby one will manifest substantial end-organ morbidities related to the presence of OSA, while all such features are absent in the other. The phenotypic variance in the clinical morbidity of OSA has therefore prompted exploration of biomarkers that would enable the identification of the more "vulnerable" patients, who would more likely benefit from timely and targeted therapeutic interventions. In other words, such studies explored the opportunity to enable incorporation of morbidity biomarkers into well-defined and validated clinical algorithms.[22] The search for appropriate biomarkers becomes therefore critical. The discovery of an ideal biomarker for OSA-associated morbidity has the potential to provide information related to prognosis and response to treatment. [5] Ideal biomarkers should be highly sensitive and specific for OSA-induced end-organ dysfunction, should be involved in an important causal pathway, so that changes in the biomarker levels in the context of OSA treatment reliably predict improvements in the specific end-organ outcome.[23]

Several different morbidity biomarkers have been proposed for OSA over the last 12 years. However, to the best of our knowledge, no scoping review has thus far been conducted to understand what we know about the use of biomarkers in the identification and management of OSA-associated morbidities. Therefore, the purpose of this scoping review was to map our current understanding regarding any of the putative biomarkers that have been thus far investigated regarding their potential association or predictive ability of OSA-associated morbidities in both adults and children, to identify gaps in the research, and to determine the value of conducting a full systematic review related to this topic.

2 Methods

This scoping review was performed while adhering to Arksey and O'Malley's scoping review proposed reporting framework. [24]

2.1 Research question

A scoping review of studies in subjects with OSA that evaluated the potential diagnostic value of biological markers (blood, exhaled breath condensate (EBC), salivary, and urinary) in the identification of those patients with morbidities associated with the underlying disease was undertaken.

2.2 Identifying relevant studies

Inclusion criteria

Retained articles were only those studies which objective was to identify morbidity-related biomarkers in patients with OSA (cognitive, excessive sleepiness, cardiovascular, and/or metabolic), with the diagnosis being confirmed with a full overnight polysomnography (PSG) in either the laboratory or home setting. Only studies that performed PSG in all subjects were included. Studies that assessed the impact of treatment were also included. Lack of a control group was accepted. Only studies in English, Spanish and Portuguese were considered.

Exclusion criteria

Studies using daytime PSG or respiratory polygraphy were not considered. Studies in which the cohort included syndromic patients (e.g., Down syndrome, craniofacial anomalies, neuromuscular disorders, etc.) or patients with a primary disease for which OSA prevalence is being investigated (e.g., patients with kidney disease, and/or rheumatologic conditions), were discarded. Reviews, letters, conference abstracts and personal opinions were not considered. Studies about central apnea were not included.

In phase 2, we excluded studies that explored OSA only, but did not assess OSA-associated morbidities.

Detailed individual search strategies for each of the following bibliographic databases were developed: Cochrane, EMBASE, MEDLINE, PubMed, and LILACS. A partial grey literature search was undertaken using Google Scholar. The end search date for all database searches was March 20, 2014. The references cited in the selected articles were also checked for any references that could have been missed during the electronic database searches. Additional studies that were already known by the authors but were not identified in the searches were also included.

Appropriate truncation and word combinations were selected and were adapted for each database search. (Appendix A) All references were managed by reference manager software (RefWorks – COS, a business unit of ProQuest, LLC. ©7200 Wisconsin Avenue, Suite 601 Bethesda, MD 20866 USA) and duplicate hits were removed.

2.3 Study Selection

The selection was completed in two phases. In phase 1, two reviewers independently reviewed the titles and abstracts of all identified electronic database citations (GDL and CPP). A third author was involved when required to make a final decision (SA). Any studies that appeared not to fulfill the inclusion criteria were discarded. In phase 2, the same selection criteria were applied to the full articles to confirm their eligibility. The same two reviewers (GDL and CPP) independently participated in phase 2. The reference list of included articles was revised by one examiner (GDL). The articles selected were read by both examiners (GDL and CPP). Any disagreement in either phase was resolved by discussion and mutual agreement between the three reviewers (GDL, CPP, SA). A fourth author, expert in sleep medicine (DG) was involved when controversy arose before making a final decision. Final selection was always based on the full-

text of the publication.

2.4 Charting the data

For the included studies the following information was recorded: year of publication, author, country, sample characteristics, name and type of OSA-related morbidity biomarkers, OSA diagnostic cut-off value at PSG, results and main conclusion. Authors of potentially eligible full-articles were contacted as necessary to provide further details about their studies.

One author (GDL) collected the required information from the selected articles. A second author (CPP) crosschecked all the collected information. Again, any disagreement in either phase was resolved by discussion and mutual agreement between the three reviewers (GDL, CPP, SA). A fourth author (DG) was involved, when required, to reach the final decision.

2.5 Level of Evidence

The methodology of selected studies was classified using a non-validated adaptation of the evidence quality criteria from American Academy of Pediatrics [25]. Two reviewers (GDL and CPP) independently classified the studies as A (well-designed prognostic or diagnostic studies on relevant population), B (prognostic or diagnostic studies with minor limitations, overwhelmingly consistent evidence from observational studies), C (observational studies (case-control and cohort design)). Disagreements were solved by a third reviewer (DG).

Additionally, the biomarker clinical application was classified as (1) potential clinical biomarker(s) of OSA morbidity; (2) inconclusive for clinical biomarker of OSA morbidity, and (3) evidence not supportive as potential biomarker(s). Two reviewers (GDL and CPP) independently classified the clinical application of biomarkers. A third reviewer (SA) revised the classification. Disagreements were further resolved by a fourth reviewer (DG).

2.6 Collating, summarizing and report the results

Any outcome measurement was considered (risk ratio (RR), odds ratio (OR) or risk difference for dichotomous outcomes; mean difference or standardized mean difference for continuous outcomes; sensitivity and specificity in diagnostic studies).

3 Results

3.1 Study Selection

During the initial phase, 572 citations were identified across the five electronic databases. After removing the duplicates articles, only 279 remained. A comprehensive evaluation of the abstracts resulted in the retention of 183 articles after phase 1. In addition 40 citations were identified in Google Scholar; however, only 4 of those citations met phase 1 inclusion criteria. One additional study was identified from the hand-search of reference lists of these studies. Six more studies were added from a content expert. Therefore, the final phase I count was 194 articles, including the 6 referred by an expert. After a full-text review, 146 studies were excluded. Reasons for exclusion can be found in Appendix B. At the end of the selection process only 48 articles were retained. A flow chart of the process of identification, inclusion, and exclusion of studies is shown in Figure 1.

Add Figure 1 here

3.2 Study Characteristics

The selected studies were grouped into two categories: children and adults. Thirty-four studies [3,4,6,7,10,15,26-53] were conducted in adults and 14 in children [2,8,9,13,14,54-62].

The pediatric studies were published between 2007 and 2013 They were conducted in United States[2,8,9,13,14,58-62],[56,57], China[55] and Egypt[54]. The OSA diagnostic criterion was established by AHI, OAI or RDI. When the authors used AHI, the diagnostic AHI ranged from AHI>1 to AHI >2 per hour of total sleep time (/hrTST). The majority of these studies assessed blood biomarkers, except for one study that studied blood and urinary biomarkers[9], one that studied urinary biomarkers[59], and one EBC[54]. In children, studies primarily focused cardiac diastolic dysfunction, insulin resistance, cognitive functional morbidity, enuresis, and vascular dysfunction. A summary of these studies' descriptive characteristics can be found in Table 1 and

Appendix C.

The studies in adults were published between 2002 and 2014. The majority was published in the United States[26,28,45,46,53], Turkey[6,29,30,43], and Japan[42,44]. The OSA diagnostic criterion was established by AHI or RDI. When the authors used AHI, the AHI ranged from AHI >5 to AHI ≥30/hrTST. Most of these reports studied blood biomarkers, three studies used both blood and urine[3,48,53], one used blood and saliva[7], and one EBC[41]. Major morbidities explored were CVD and cerebrovascular injury. A summary of these studies' descriptive characteristics can be found in Table 2 and Appendix D.

Add Table 1 and Table 2 here

3.3 Level of Evidence

Almost all pediatrics studies were classified as B (prognostic or diagnostic studies with minor limitations, overwhelmingly consistent evidence from observational studies). Only one study was classified as C (case-control and cohort design)[14] and two studies were classified as A (well designed prognostic or diagnostic studies on relevant population)[8,61]. None of the studies however performed ROC analysis for their biomarkers of interest, except Kheirandish-Gozal et al[59] who explored combinatorial biomarker approaches using specific cut-offs for levels of urinary neurotransmitters and their overnight changes.

In adult studies, 29 studies were classified as B[3,4,6,7,10,15,26-53]. Five studies were classified as C [4,28,38(Kato, 2011 #82,44,50]. None of the studies was classified as A.

Synthesis of Results

Thirty-one potential biomarkers were identified. Only two (hsCRP and IL-6) were evaluated in both adults and children (Table 3). Only one study[59] reported diagnostic test accuracy (DTA) measurements about the biomarkers evaluated. Kheirandish-Gozal[59] performed a neurocognitive battery assessing general cognitive ability (GCA) to explore overnight changes in

neurotransmitters in the urine in children with and without OSA. They concluded that pediatric OSA is associated with overnight increases in urinary concentrations of catecholamines and that combinatorial approaches using defined cutoffs in overnight changes in concentration of selected neurotransmitters in urine may predict both OSA and the presence of cognitive deficits.

Among the 17 countries that have been published about this topic, most of the studies originated from the USA (Table 4).

Add Tables 3 and 4 here

4 Discussion

The present scoping review investigated the available evidence aiming to identify biomarkers in subjects with OSA-associated morbidities.

OSA is one of the important independent risk factors for CVD [5-7], including hypertension [4], cerebrovascular disease [33], and endothelial dysfunction [2,3] with diabetes[63], cognitive dysfunction[8], excessive daytime sleepiness (EDS)[14,15] being also investigated, albeit less frequently. The risk of mortality was pronounced particularly in those with moderate-to-severe OSA. The existence of OSA associated with morbidities provides the need to develop different and likely combined therapeutic approaches according to the patient phenotypic complexity. The close association between OSA and comorbidities may magnify the cardiovascular risk factors, aggravating mortality.[64]

The overnight PSG has been considered as the actual gold standard for OSA diagnosis. However, one of its major limitations resides in its inability to accurately identify those patients with OSA who manifest end-organ morbidity as a consequence of the underlying OSA. A method allowing for the screening of OSA patients in a large scale, and enabling an accurate identification of those patients with specific morbidities could potentially revolutionize the field.[65] This urgent need to find an ideal biomarker for OSA specific morbidities could explain the large amount of studies that have somewhat addressed this topic since 2000. The ideal biomarker should have some characteristics, such as morbidity specificity, presence in all patients with the end-organ dysfunction of interest, reversibility following proper treatment, and detectability before patients develop several clinical manifestations. It should also reflect the severity of the clinical morbid manifestation, and provide an indicator of cumulative injury over time, as well as exhibit minimal overlap between no morbidity and morbidity. [66]

Different groups of researchers have tried to identify morbidity-related biomarkers in children and adults with OSA throughout the world. The United States leads in such efforts in both adults and children. Interestingly, in some countries such as Turkey and Japan, studies have been performed studied in adults, but not in children.

It is also noteworthy the wide range variation in OSA diagnostic criteria. AHI is the most frequently used marker of OSA severity. Nevertheless, the use of AHI is associated with two major limitations. Firstly, the clinically valid cut-off for normal AHI is unclear in children. Secondly, no consensus has been achieved as to whether children with AHI values between the normal cut-off (<1/hrTST) and 5/hrTST should undergo adenotonsillectomy. [66] It is therefore difficult to define OSA when exclusively using PSG-based criteria, a problem that has led to several experts and even clinical practitioners to state that "you will know that OSA is present when you see it". This lack of consensus in the diagnostic criteria is the result of the relative dichotomy between PSG-derived measures and clinical symptoms. Children who are very symptomatic may present a "normal PSG" in the presence of habitual snoring. Conversely, asymptomatic snoring children may have concurrent and severe respiratory disturbance in their PSG. [67] To overcome some of this debate, the American Academy of Sleep Medicine (AASM)[68] has set a threshold of 15 events per hour with or without symptoms or 5 events per hour with symptoms for the diagnosis of OSA in adults [69]

Interestingly, the majority of studies evaluated blood biomarkers. Few studies evaluated saliva, urine and/or EBC, a surprising finding considering that these approaches are noninvasive and are easily collected, especially in children.

When analyzing the level of evidence, only two studies were classified as A.[8,61] To assess the magnitude of the systemic inflammatory response, as measured by high-sensitivity C-reactive

protein (hsCRP) serum levels, that may identify children with OSA at higher risk for cognitive morbidity, Gozal et al 2007[8] recruited habitually snoring children and non-snoring children from the community. All children underwent PSG and neurocognitive testing and a fasting blood draw the next morning. Snoring children were divided into OSA and non-OSA groups, and children with OSA were further subdivided into those with two or more abnormal cognitive subtests and those with normal cognitive scores. Gozal and colleagues [8] concluded that hsCRP levels are higher in children with OSA, and particularly in those who develop neurocognitive deficits, suggesting that the magnitude of the inflammatory responses elicited by OSA is a major determinant of increased risk for neurocognitive dysfunction. Indeed, among the 103 snoring children without OSA, hsCRP levels were 0.19 ± 0.07 mg/dl (p value not significant vs. control children). However, 12 of the snoring children without OSA exhibited cognitive deficits and their hsCRP levels were 0.33 ± 0.10 mg/dl ($p < 0.04$ vs. habitual snorers with normal cognitive scores). Among the 102 children with OSA, 57 had evidence of abnormal cognitive function, and these children were those whose hsCRP levels, namely 0.48 ± 0.12 mg/dl, markedly differed from not only control children ($p < 0.0001$) or snoring children (($p < 0.0001$), but also from the OSA children with preserved cognitive abilities (0.21 ± 0.08 mg/dl; $p < 0.002$). [8] Gozal [61] recruited children from the community and underwent overnight PSG to test if the lower IGF-1 serum levels in children with OSA would be associated with more severe neurocognitive morbidity compared with matched controls. They concluded that IGF-1 levels are higher in OSA children, mainly in those who do not manifest neurocognitive deficits.

Potential biomarkers in children have mainly focused on the investigation of myeloid-related protein (MRP) 8/14, and urinary neurotransmitters. On the other hand, studies in adults with OSA have focused on hsCRP and IL-6, and the latter 2 candidates were the only ones evaluated in both

adults and children. We should emphasize that only one study presented DTA measurements, even if it is now widely recognized that the lack of DTA results is concerning and should not be viewed as acceptable in biomarker studies.[70] However, the findings reported herein could provide the basis for future multicenter research efforts. In addition, there is a critical need for future studies to assess and provide a cut-off value for each of the biomarkers being evaluated and thus enable comparisons across studies as well as across age groups (e.g., adults vs. children). Notwithstanding such considerations, it is worthwhile to point out that the retained potential morbidity-related biomarkers, as determined from this analysis are suggestive that the magnitude of inflammatory responses to OSA is a major contributing mechanisms to end-organ morbidity. Thus, these findings further reinforce the now well-established conceptual framework that OSA is a low grade systemic inflammatory disease.

In summary, this scoping review provides insights into our current state of knowledge about biological markers and their applicability in the detection of OSA-induced morbidity. Over the last 12 years, a substantial number of studies have aimed to identify an ideal biomarker for OSA morbidity. The most promising biomarkers identified revolved around the identification of CVD in OSA patients. The 48 studies identified in this scoping review should be helpful in identifying appropriate questions in the field and formulate adequate research strategies in this important area.

Limitations

The absence of a unique PSG criterion for the diagnosis OSA may lead to different interpretations of the findings in the studies included in this review. The studies included here explored different types of morbidities such that the critical mass of studies addressing a specific morbidity is unlikely. Most studies used a clinical referral sample with no *post-hoc* verification in

more generalized community settings. Importantly, the duration of OSA was now evaluated and included as a potential confounder to the validity of any of the putative biomarkers. Furthermore, considering that some gender-related differences in urinary biomarkers aiming at diagnosing OSA in children have been reported, [71] it would be interesting and potentially relevant to explore gender as a modifier of the receiver-operator curve properties of selected biomarkers. Finally, the majority of studies have been performed in the United States, such that extrapolation to other populations is uncertain.

5 Conclusions

Blood-based biomarkers accounted for the majority of the studies, and most of the explored approaches did not identify definitive biomarkers of OSA morbidity. IL-6 and hsCRP appear to exhibit a favorable profile as biomarkers aiming to discriminate OSA patients with and without morbidity in adults, as well as MRP 8/14 in children. Urinary neurotransmitters can potential be a good tool for screening cognitive function in OSA children.

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Figure 1 - Flow Diagram of literature search and selection criteria[1].

[1] Adapted from PRISMA.

Table 1 - Summary of study descriptive characteristics of included pediatric articles (n=6). The biomarker clinical application was classified as (1) potential morbidity biomarker(s) in OSA patients, (2) inconclusive as biomarker, and (3) evidence not supportive as potential biomarker(s). The level of evidence was classified in A (well designed prognostic or diagnostic studies on relevant population), B (prognostic or diagnostic studies with minor limitations, overwhelmingly consistent evidence from observational studies), C (observational studies (case-control and cohort design) (n=14)

Year	Author	Country	Cases	Control	Mean Age or range if provided	Morbidity	Biomarker Type	OSA diagnostic criteria (PSG)
2007	Gozal et al [62]	United States	Snoring children divided in 2 groups: Non-OSA (n=112/62 male) and OSA (n=146/79 male)	Non-snoring children (n=87/47 male)	5-7	Cognitive dysfunction	Blood	OAI> 1 and AHI > 2
2007	Gozal et al [8]	United States	Total (n=205) Snoring Non-OSA (n=103/57 male) Snoring OSA (n=102/59 male)	Non-snoring with AHI <1 (n=73/40 male)	5-7	Cognitive dysfunction	Blood	AHI >1 and/or AHI > 2
2008	Biltagi et al [54]	Egypt	Children with adenoidal hypertrophy OSA suspected (n=40)	Healthy children (n=20)	4-8	Cardiac Diastolic dysfunction	EBC	clinical assessment score ≥40
2008	Sans Capdevila et al [13]	United States	OSA children (n=20) HS children (n=20)	Controls (n=20)	5-7	Enuresis		OAI> 1 and AHI > 2
2009	Gozal et al [61]	United States	Snoring children: Non-OSA (n=23/13 male) OSA (n=87/46 male)	Non-snoring (n=52/28 male)	5-7	Cognitive dysfunction	Blood	OAI>1 and/or AHI > 2 with a nadir oxygen saturation value at least <92%
2010	Gozal et al [14]	United States	OSA children (n=15)	Non-OSA (n=15)	7.3#	EDS	Blood	AHI ≥1
2010	Gozal et al [56]	United States	OSA children (n=87/51 male)	Non-snoring (n=21/11 male)	5-8	Neurocognitive and Endothelial Dysfunction	Blood	OAI≥ 1 and AHI ≥ 5
2010	Kelly et al [9]	United States	OSA suspected children: Pre-pubertal (n=20/11 male) Pubertal (n=34/21 male)	Non-OSA Pre-pubertal (n=17/12 male) Pubertal (n=27/12 male)	4-18	Insulin Resistance	Blood /urine	AHI >1.5
2010	Kheirandish-Gozal et al [58]	United States	OSA children (n=80)	Non-OSA (n=20)	8.2	Vascular Dysfunction	Blood	OAI≥ 1 and AHI ≥ 5
2010	Kim et	United	OSA (n=140/85 male#)	Non-OSA	7.6	Endothelial	Blood	AHI ≥ 1

	al [60]	States		(n=115/64 male#)		dysfunction		
2010	Kim et al [57]	United States	Mild OSA (n=85) Moderate-to-severe OSA (n=26)	Non-OSA (n=102)	7.7	emtabolic and endothelial dysfunction	Blood	AHI ≥ 1
2010	Wang et al [55]	China	OSA (n=44/28 male)	Non-OSA (n=26/15 male)	6.3#	Cognitive dysfunction	Blood	RDI ≥ 5
2011	Kim et al [2]	United States	Mild OSA (n=65/42 male) Moderate to severe OSA (n=14/9 male)	Non-OSA (n=56/30 male)	4-12	Endothelial dysfunction	Blood	AHI >1
2013	Kheirandish-Gozal et al [59]	United States	OSA children (n=50/27 male#))	Non-OSA (n=20/11 male#)	6-12	Cognitive dysfunction	Urine	AHI ≥ 2

All terms that mean obstructive sleep apnea (SDB, SRDB, OSAS) were standardized as OSA. # Mean calculated by author.

A&T=adenotonsillectomy, AHI=apnea/hypopnea index, APO=apolipoprotein, BMI=body mass index, BNP=brain natriuretic peptide levels, BNDF= Brain-Derived Neurotrophic Factor, cICAM-1=circulating intercellular adhesion molecule 1, CRP=C reactive protein, EBC= exhaled breath condensate, EDS=excessive daytime sleepiness, EPCs=endothelial progenitor cells, Hs-CRP= high sensitivity C-reactive protein, IGF=insulin growth factor, IL-6=interleukin-6, MPs=microparticles, MRP=myeloid-related protein, OSA=obstructive sleep apnea, RDI= respiratory disturbance index, TNF-α= tumor necrosis factor alpha.

Table 2 - Summary of study descriptive characteristics of included articles (adults, n=33). The biomarker clinical application was classified as (1) potential biomarker(s) of OSA-associated morbidity; (2) inconclusive for morbidity biomarker, and (3) evidence not supportive as potential morbidity biomarker(s). The level of evidence was classified in A (well designed prognostic or diagnostic studies on relevant population), B (prognostic or diagnostic studies with minor limitations, overwhelmingly consistent evidence from observational studies), C (observational studies (case-control and cohort design) (n=34)

Year	Author	Country	Cases	Control	Mean Age or range if provided	Morbidity	Type of Biomarker	OSA diagnostic criteria (PSG)
2002	El-Solh et al [26]	United States	Patients with moderate to severe OSA (n=15) matched with controls by age, gender, BMI, and severity of CAD	Non-OSA (n=15)	61.2	CAD	Blood	AHI ≥10/h
2002	Jordan et al [27]	Germany	OSA patients (n=19/19 male) divided in 2 groups: Group 1: patients with OSA without severe hypoxemia during sleep Group 2: patients with OSA with severe hypoxemia during sleep	-	50.6	Cerebrovascular injury	Blood	RDI>40/h
2004	Gami et al [28]	United States	Patients with moderate to severe OSA (n=15/15 male)	-	62.0	CAD	Blood	AHI>15/h
2005	Kokturk et al [29]	Turkey	Group 1: Patients with OSA and CVD (n=38) Group 2: Patients with OSA without CVD (n=56)	Group 3: patients without OSA with CVD (n=57)	45.0#	Cardiovascular morbidity	Blood	AHI≥5/h
2006	Kokturk et al [30]	Turkey	Group 1: OSA obese patients with CVD (n=25) Group 2: OSA patients without CVD (n=47) Matched with controls by age and BMI	Group 3: Non-OSA obese with CVD (n=42)	49.7#	Cardiovascular morbidity	Blood	AHI≥5/h
2006	Saletu et al [31]	Austria	Group 1: mild OSA (n=27) Group 2: moderate OSA (n=25) Group 3: severe OSA (n=51)	Non-OSA (n=44)	53.5#	Cerebrovascular disease	Blood	AHI≥5/h
2007	Bostrom et al [4]	Sweden	Hypertensive patients in primary care (n=157)	Normotensive	61.0#	Hypertension and cardiovascular	Blood	AHI≥10/h

				population controls (n=181)		complications		
2007	El Solh et al [32]	United States	OSA (n=14)	Non-OSA (n=10)	44.4#	Atherosclerosis	Blood	AHI>5/h
2007	Minoguchi et al [33]	Japan	OSA (n=50/50 male) Matched with control by age and weight	Non-OSA obese patients (n=15)	48.9#	Cerebrovascular disease	Blood	AHI≥5/h
2007	Pena Bravo et al [34]	Spain	OSA (n=50/50 male) Matched by age with controls Without personal or family history of CVD or diabetes	Non-OSA (n=20)	50.3#	Daytime sleepiness	Blood	AHI≥20/h
2008	Da Silva et al [35]	Brazil	Morbidity obese (n=25/10 male) with OSA complaints	-	39.9	Cerebral injury	Blood	AHI≥5/h
2008	Hubner et al [36]	Germany	OSA suspected (n=60)	-	55.7	Cardiovascular stress and dysfunction	Blood	AHI≥5/h
2008	Mills et al [37]	South Korea	Untreated OSA (n=56/41 male)	-	49.2	Fatigue	Blood	AHI≥15/h
2008	Ursavas et al [38]	Turkey	OSA (n=22)	Non-OSA (n=18)	47.8#	Obesity	Blood	AHI≥5/h
2009	Al Lawati et al [39]	Canada	OSA (n=176/119 male)	-	50.0	Cardiovascular disease	Blood	AHI≥5/h
2009	Koyama et al [40]	Brazil	OSA (n=266/266 male) divided in 2 groups: Normotensive (n=152) Hypertensive (n=114)	-	48.0	Angiotensin-converting enzyme (ACE) polymorphism	Blood	AHI>5/h
2009	Papanas et al [11]	Greece	OSA (n=31/31 male)	-	46.7	Diabetes	Blood	AHI>15/h
2010	Culla et al [41]	Italy	OSA (n=39)	Non-OSA non smoking with	53.8#	Oropharyngeal inflammation	EBC	AHI>5/h

				CRS (n=15) and Non-OSA non-smoking with mild asthma (n=26)				
2011	Aihara et al [42]	Japan	OSA: Mild OSA (n=25) Moderate OSA (n=52) Severe OSA (n=73)	Non-OSA (n=20)	53.8#	Lung injury	Blood	AHI>5/h
2011	Bekci et al [43]	Turkey	Group 1: Below the median arousal Group 2: Above the median arousal	-	43.5	Cardiac and vascular events	Blood	AHI≥5/h
2011	Kanbay et al [6]	Turkey	OSA Mild OSA (n=17) Moderate OSA (n=34) Severe OSA (n=93)	Non-OSA (n=22)	54.2#	Cardiovascular disease	Blood	AHI>5/h
2011	Kato et al [44]	Japan	(n=267/233 male)	-	51.0	Renal dysfunction	Blood	AHI≥5/h
2011	Mohsenin and Urbano [45]	United States	OSA Normotensive OSA (n=11/10 male) Hypertensive OSA (n=11/10 male)	-	46.5#	Hypertension	Blood	AHI≥30/h
2011	Rahangdale et al [46]	United States	OSA obese non-smokers (n=47) Matched with controls by BMI	Non-OSA obese non-smokers (n=30)	38.7#	Platelet activation	Blood	AHI≥10/h
2011	Sanchez-de-la torre et al [15]	Spain	OSA with EDS (n=132/110 male) Matched by age, gender, BMI, AHI with controls	OSA without EDS (n=132/113 male)	50.5#	EDS	Blood	AHI≥20/h
2011	Zhao et al [47]	Australia	OSA Mild OSA (n=50/45 male) Moderate OSA (n=43/38 male)	Non-OSA (n=25/20 male)	58.7#	Coronary artery disease	Blood	AHI≥5/h

			Severe OSA (n=33/27 male)					
2012	Celec et al [7]	Slovakia	OSA (n=89/67 male)	-	56.1	Cardiovascular disease	Blood, saliva	RDI>30
2012	Del Ben et al [3]	Italy	OSA Mild/moderate OSA (n=61) Severe OSA (n=30)	Non-OSA snorers (n=47)	53.7#	Endothelial dysfunction and oxidative stress	Blood, urine	(home PSG) AHI≥5/h
2012	Oyama et al [52]	Japan	OSA + Mets patients (n=32/19 male) who received CPAP therapy for 3 months	-	53.9	Metabolic syndrome	Blood	AHI>20/h
2013	Cherneva et al [48]	Bulgaria	OSA: Diabetic OSA patients (n=23/17 male) Impaired glucose tolerance (n=27/23 male) Normal glucose metabolism (n=17/17 male)	-	49.8#	Diabetes	Blood, urine	AHI≥5/h
2013	Cholidou et al [49]	Greece	OSA Moderate OSA (n=33/25 male) Severe OSA (n=27/26 male)	Non-OSA (n=14/12 male)	45.2#	Cardiovascular disease	Blood	AHI>5/h
2013	Sales et al [50]	Brazil	OSA (n=14) Matched by years of schooling, age, BMI with controls	Non-OSA (n=13)	36.0	Neuropsychological performance and oxidative stress	Blood	AHI>10/h and at least one symptom or AHI >15/h
2014	Paik et al [53]	South Korea	Sleepy OSA (n=26/19 male)	Non-sleepy OSA(n=23/18 male)	45.5#	EDS	Urine	AHI>5
2014	Salord et al [51]	Spain	Mets Mets Non-OSA (n=13/5 male) Mets OSA (n=26/6 male)	Non-OSA Non-Mets (n=13/4 male)	43.0#	Mets	Blood	AHI≥15/h

All terms that mean obstructive sleep apnea (SDB, SRDB, OSAS) were standardized as OSA. # Mean calculated by author.

8-iso-PGF2α=8-iso-prostaglandin F2 α, ACE=Angiotensin converting enzyme, ADMA=asymmetrical dimethylarginine, AGEs=advanced glycation end products, AHI=apnea/hypopnea index, AOPP=advanced oxidation protein products, BMI=body mass index, CAD=coronary artery disease, CD146=melanoma cell adhesion molecule, CPAP=continuous positive airway pressure, CRP=C reactive protein,CRS=chronic rhinitis or rhinosinusitis,

CVD=cardiovascular disease, EBC=exhaled breath condensate, EDS=excessive daytime sleepiness, ET-1=endhothelin-1, FENO=exhaled nitric oxide, FFA=free fatty acids, FRAP= ferric reducing antioxidant power, FRAS= ferric-reducing ability of serum, GGT=serum gamma-glutamyl transferase, GPllb/llla= glycoprotein IIb/IIIa, HbA_{1c}=glycosylated hemoglobin, HDL=high density lipoprotein, Hs-CRP=high sensitivity C-reactive protein, I/D=insertion/deletion, ICAM-1=intercellular adhesion molecule 1, IL-1B=interleukin-1B, IL-6=interleukin-6, IL-8=interleukin-8, KL-6=Krebs Von den Lungen-6, LDL= low density lipoprotein, Lp-PLA2=lipoprotein-associated phospholipase A2, Mets=morbid obesity and metabolic syndrome, NOx=Nitrogen oxide, NP=neopterin, NSE=neuron-specific enolase (a glycolytic pathway enzyme from CNS), NT-ProBNP=N-terminal pro-brain natriuretic peptide, oNO=oral nitric oxide, OSA=obstructive sleep apnea, P-selectin= Platelet selectin, PGF2-α=Prostaglandin F2α, PSG=polysomnography, RDI=respiratory disturbance index, S100B=calcium binding protein B, SBI=silent brain infarction, sCD40= soluble CD40, sCD40L=soluble CD40 ligand, sEng=soluble endoglin, sFasL= soluble Fas ligand, sFlt-1=soluble fms-like tyrosine kinase-1, sICAM-1=soluble Inercellular adhesion molecule 1, sNOX2-dp=soluble NOX2 derived peptide, SP-D=surfactant protein, sP-selectin=soluble P-selectin, sTNF-RI=soluble tumor necrosis factor receptor 1, sVCAM-1= soluble vascular cell adhesion molecule-1, TAC=total antioxidant capacity , TBARS=thiobarbituric acid reactive substance, TNF-α=tumor necrose factor alpha, VCAM-1=vascular cell adhesion molecule-1, VEGF=vascular endothelial growth factor.

Table 3 - Potential biomarkers identified (n=31)

Potential Biomarkers	Children
8-isoprostane	✓
Adiponectin	✓
AGEs	
AOPP	
APOEe4	✓
Calproctectin	
Catecholamines	✓
Catestatin	✓
CRP	✓
Cystatin C	
FFA	
FRAP	
FRAS	
Fructosamine	
GGT	
IL-6	✓
IL-8	
HOMA	✓
KL-6	
Leptin	
Lipid profiles	
MRP8/14	✓
NP	
Resistin	
sTNF-RI	
S100B	
sVCAM-1	
TAC	
TBARS	
TNF- α	✓
Urinary Neurotransmitters	✓

AGEs=advanced glycation end products, AOPP=advanced oxidation protein products, hsCRP=high sensitivity C-reactive protein, FFA= free fatty acids, FRAP=ferric reducing antioxidant power, FRAS=ferric reducing ability of serum, GGT=serum gamma-glutamyl transferase,,IL-1B=interleukin 1B, IL-6=interleukin-6, IL-8=interleukin-8, HOMA=homeostatic model assessment of insulin resistance, KL-6= Krebs von den Lungen-6, MRP=myeloid-related protein**,** NP=neopterin, S100B=calcium binding protein B, sVCAM-1=soluble vascular cell adhesion molecule-1, TAC=total antioxidant capacity, TBARRS=thiobarbituric acid reactive substance, TNF-α=tumor necrosis factor alpha.

Table 4 - Distribution of studies according to country (n=17).

Country	Total	Children	Adults
United States	17	12	5
Turkey	5	0	5
Japan	4	0	4
Brazil	3	0	3
Spain	3	0	3
Germany	2	0	2
Greece	2	0	2
Italy	2	0	2
Australia	1	0	1
Austria	1	0	1
Bulgaria	1	0	1
Canada	1	0	1
China	1	1	0
Egypt	1	1	0
Slovakia	1	0	1
South Korea	2	0	2
Sweden	1	0	1
Total	**48**	**14**	**34**